Ozone therapy for low back pain. A systematic review

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ACTA REUMATOL PORT. 2018;43:172-181

ABSTRACT

Background: Low back pain associated with lumbar disc herniation is common in the general population, with evident repercussion in quality of life and a significant economic burden. Patients refractory to conservative treatment seek additional treatment and minimally invasive interventions are often proposed as valid options. Ozone therapy has been suggested as an alternative treatment due to its potential analgesic and anti-inflammatory effect.
Objective: This systematic review aims to investigate the effectiveness and safety of ozone therapy for low back pain in patients with lumbar disc herniation.
Material and Methods: A systematic search of the literature was performed in Pubmed and Scopus, followed by a three-step selection process. Data was processed by 2 independent reviewers and information was gathered based in pre-defined variables. Only articles studying humans; original and written in English; on treatment with ozone; comparing the effect ozone therapy (experimental group) with another non-ozone intervention (control group); and on patients with lumbar pain and disc hernia, were included.
Results: From 439 references retrieved after duplicates removal, inclusion and exclusion criteria were applied, and 7 studies were included in the final revision. One article compared treatment with ozone versus placebo, one ozone and global postural re-education versus global postural re-education alone, two the combination of ozone with steroid *versus* steroid alone, two ozone versus steroid and one ozone *versus* micro-discectomy. All but the study comparing ozone application with micro-discectomy, showed similar or better results in the experimental group. Only three studies evaluated the presence of side effects. In two papers no complication was reported, and in the other, a low percentage of adverse effects was observed, not significantly different between the two study groups.
Conclusions: Only a small number of poor quality studies on ozone effect in low back pain and disc herniation were available for inclusion in our review. Nevertheless, these reported an improvement in pain and functional scores with its application. Complications, mostly *minor,* but potentially serious are underreported. Additional studies with adequate and consistent methodologies are needed before the role of ozone can be established in the management of low back pain.

Keywords: Low back pain; Ozone injection; Oxygen-ozone therapy; Lumbar disc hernia

INTRODUTION

Low back pain (LBP) is a very common disorder with significant impact on patients' clinical status, and relevant socioeconomic and public health consequences[1]. The prevalence is estimated at 22-65% per year, and up to 80% of the population presents mild to severe LBP at some point in life[1]. In approximately 60-80% of cases, no specific cause is diagnosed, and the pain is attributed to muscle or ligament tension, and in only 5-15% to degenerative causes and disc injuries. Symptomatic disc herniation is a degenerative disease of the intervertebral disc that can presents with low back pain, sciatica or lumbar compressive radiculopathy with functional limitations[1]. Studies on the natural history of disc herniation show that most of the associated symptoms decrease significantly after conservative treatment[2]. Lumbar disc herniations (LDH) are also frequently detected in asymptomatic individuals who undergo additional diagnostic tests for other medical complaints, and its prevalence is estimated at 57%[3]. LDH is therefore a relatively common condition with a favorable prognosis in most cases[4]. Still LDH is the most fre-

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quent indication for surgery of the spine. Although good results can be expected, the reoperation rate is between 7-9% at 2 years and increases to 10-25% at 10 years postoperatively[5]. Up to 20% of patients maintain pain after surgery, and recurrences of LDH, as well as adhesion phenomena, post-surgical scars and fibrosis, may require new surgical intervention, which in turn can produce acute symptomatology with instability of the spine[6, 7]. Therefore, different minimally invasive, well-tolerated and low-cost procedures have been developed to provide good clinical results without the associated drawbacks of surgery[1]. Ozone, the triatomic form of oxygen, is a strong oxidant, capable of inducing several useful biological responses and, eventually, reversing chronic oxidative stresses such as those derived from degenerative processes[8]. Using the ability of ozone to cleavage proteoglycans and neutralize the negative charge of sulfate side chains, water retention can be diminished, resulting in a reduction of the volume of the hernia[5]. Intradiscal ozone injection was first proposed in Italy in the 1980s as a treatment for herniated disc[5]. A mixture of ozone and oxygen (O2O3) can be injected directly in the disc or indirectly in the paravertebral muscles aiming to reduce herniation, relieving nerve root compression, with potential analgesic and anti-inflammatory effects[8,9]. It is currently used in many European, Asian ant South American countries as a minimally invasive approach to treat LDH refractory to conservative treatment, or for those with contraindications for surgery[3]. Despite its increasing popularity, the scientific data regarding both its effectiveness and safety is scarce, and adequately performed randomized controlled trials (RCTs), and meta-analysis are definitely needed[8,10,11]. The aim of this systematic review is to investigate the effectiveness and safety of ozone therapy for low back pain and lumbar disc herniation.

MATERIAL AND METHODS

A systematic search was conducted in Pubmed and Scopus, using as a query, a combination of ("ozone therapy" or "ozone" or "ozone nucleolysis") and ("chronic low back pain" or "back pain" or "pain" or "spine" or "vertebra" or "column" or "disc" or "disc hernia"). Subsequently a selection process was carried out in three stages. The data was processed by two independent reviewers and the information was collected based on pre-defined variables. In the first step, titles and abstracts were selected, and articles proceeded to the second stage after the inclusion by at least one reviewer. Within the second stage, full-text was evaluated and the disagreements were discussed among reviewers. Inclusion criteria were: articles studying humans; original and English written articles; articles on treatment with ozone; articles comparing the result of ozone therapy (experimental group) with another non-ozone intervention (control group); on patients with lumbar pain of degenerative causes. All those whose patients had other known conditions rather than degenerative lumbar changes (i.e. inflammatory or infectious arthritis, neoplastic conditions) were excluded. When the full text was not available, the authors were asked for full text copy. One article was excluded due to unavailability of the full text. Two comparison groups were previously defined based in data gathered from each individual article, an experimental group, which received ozone, and a control group that receives the same treatment without ozone. Data on demographics, diagnosis, treatment and ozone application and clinical and/or radiologic assessments was collected. When available, data on significance of each study was also pooled, with a statistically significant value defined as $p < 0.05$. This review was performed based on Items Preferred Reports for Systematic Reviews and Guidance Indicators for Meta-Analyzes (PRISMA)[12]. PRISMA checklist is available on Supplementary File.

RESULTS

From 439 references retrieved after duplicates removal, inclusion and exclusion criteria were applied, and 7 studies were included in the final revision (Table I, Figure 1). Two articles on ozone versus steroid, two on the combination of ozone with steroid versus steroid alone, one on ozone versus a sham procedure, one on ozone versus microdiscectomy, and another one on ozone versus global postural re-education (GPR), and ozone and GPR versus GPR alone. Follow-up times from individual studies ranged from 2 weeks to 5 years. Different injection routes and ozone concentrations were used in the studies included. All performed at least a clinical evaluation such as Visual Analog Scale (VAS) for pain, Oswestry Disability Index (ODI) and McNabb method, and 4 also underwent a complementary assessment with Computed Tomography (CT) and/or Magnetic Resonance Imaging (MRI). Apart

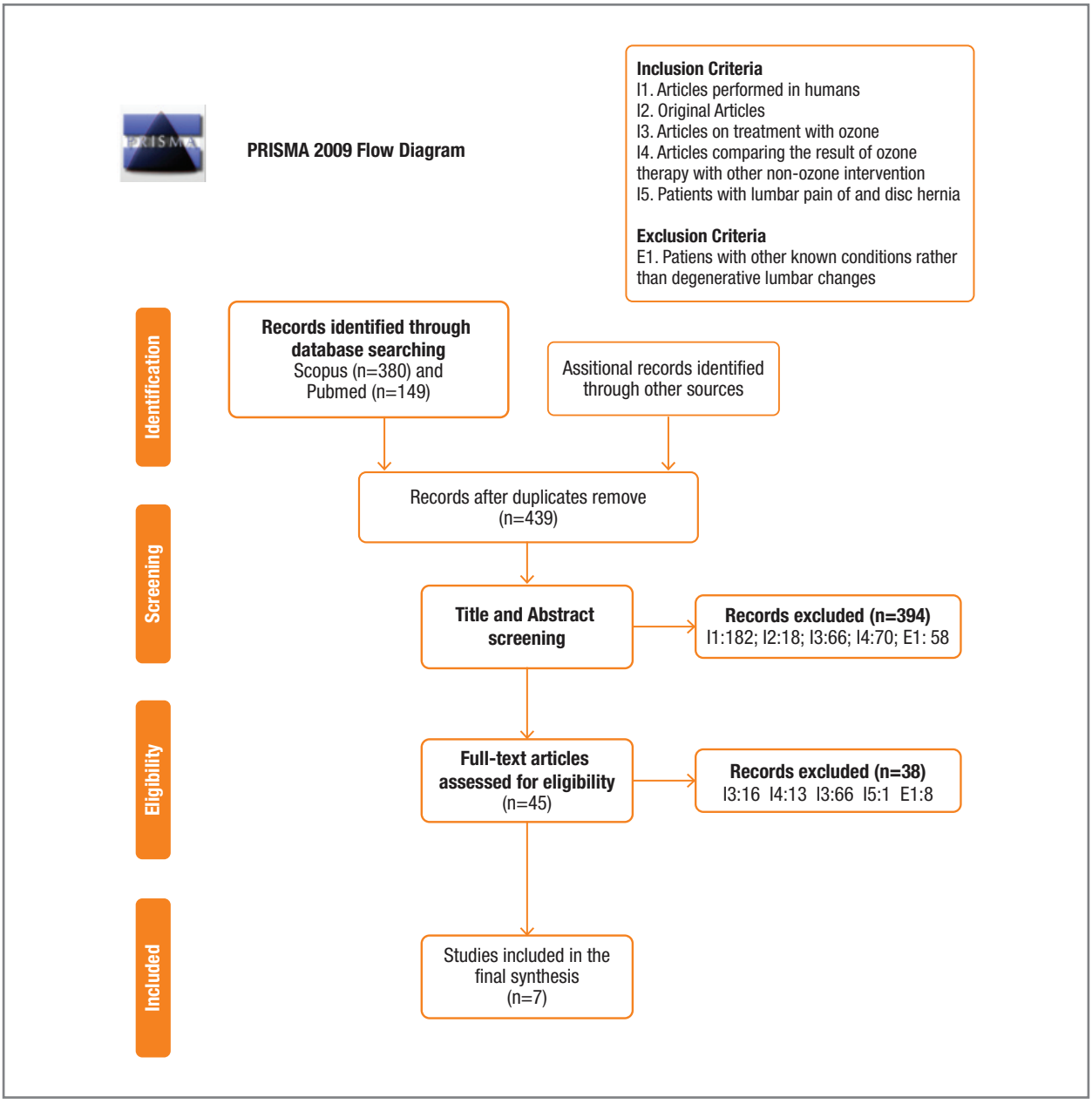

FIGURE 1. PRISMA flow diagram of article selection.
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

from the study comparing ozone application with micro-discectomy, all studies showed similar or better results in the experimental group. In particular, evolution of pain was assessed in all articles, with six reporting a significant decrease in the experimental group in at least one study time. On the other hand, in the two studies that reported on functional assessment, only one observed a significant improvement in some of the clinical scores applied (Table II). Only three authors reported the incidence of side effects. In two papers no patient from either study group suffered any complication, and in the other, authors stated a low percentage of adverse effects, not significantly different between the two study groups (Table I and II).

TABLE I. DATA FROM INDIVIDUAL STUDIES

ID	Age (mean ± SD)	N (E/C)	Gender (M/F)	Experimental Group		Control Group		Clinical Assessment	Other Assessments	Study Times	Side Effects % (E/C)
Zambello, 2006	E: 51±6.1; C: 48±3.2	351 (180/171)	191/160	Ozone	5 mL paravertebral injection (10-20 mg/mL)	Steroid	80mg triamcinolone epidural injection	Pain: McNabb method (excelente/ /good)	NA	3w; 6m	NI
Bonetti, 2005	48	306 (86/80)	128/178	Ozone	3mL intraforaminal injection (25mg/mL)	Steroid	80 mg methylprednisolone periradicular injection	Pain: McNabb method (excelente/ /good)	NA	1w, 3m, 6m	NI
Perri, 2015	E: 44.4±9.5; C: 43.8±11.2	154 (77/77)	NI	Steroid+ Anesthetic + Ozone	Similar to control + 10 mL intradiscal and intraforaminal ozone injection (28 mg/ml)	Steroid + Anesthetic	2-3mL of betamethasone Intraforaminal and epidural injection (4mg/2ml) + 2-3mL ropivacaine 2%	Pain: VAS	MRI (T2 shine--through effect; DWI signal)	2m, 4m, 6m	NI
Galluci, 2007	E: 48.8±13.6; C: 47.2±11.9	159 (82/77)	88/71	Steroid + Anesthetic + Ozone	Similar to control + 10-14mL intraforaminal and intradiscal ozone injection (28 mg/mL)	Steroid + Anesthetic	2mL triamcinolone intraforaminal and intradiscal injection (40 mg/mL) + 2-4mL ropivacaine 2%	Functional: ODI (>20% positive variation)	NA	2w, 3m and 6m	0/0
Paoloni, 2009	18-65#	60 (36/24)	28/32	Ozone	20 mL intramuscular paravertebral infiltrations (20 mg/mL) – 15 times	Sham procedure	Sham procedure	Pain: VAS, Functional: SF-36 Backill, Kellner, Drug assumption	MRI (reduction in disc hernia)	2w, 4w, 6w, 3m, 6m	0/0
Paradiso, 2005	30-60#	300 (150/150)	152/148	Ozone	Percutaneous discolysis	Micro- -discectomy	NI	Pain: VAS Functional: ODI	EMG, CT/MRI (reduction in disc hernia)	4-6m, 1y, 3y	NI

continues on the next page

TABLE I. CONTINUATION

ID	Age (mean ± SD)	N (E/C)	Gender (M/F)	Experimental Group		Control Group		Clinical Assessment	Other Assessments	Study Times	Side Effects % (E/C)
	E: 50.3±13.5 C: 46.1±13.2	546 (109/54)	279/267	Ozone	Ozone: 15 mL intramuscular paravertebral injection (20 mg/mL) (12 biweekly + 10 maintenance sessions)	GPR	Breathing, stretching and proprioception exercises (12 biweekly sessions of + 3 maintenance sessions)	GPR	MRI (reduction in disc hernia) Recurrence	1m, 3m	0.9/NI
	E: 50.5±14.2 C: 46.1±13.2	546 (383/54)		Ozone + GPR							1.6/NI

E: Experimental; C: Control; w: weeks; m: months; y: years; NA: Not Assessed; NI: No Information; NC: No Comparison; VAS: Visual Analogue Scale; SF-36: Short Form 36 Questionnaire; ODI: Oswestry Disability Index; MRI: Magnetic Resonance Imaging; CT: Computed Tomography; EMG: Electromyogram; GPR: Global Postural Re-education. #Min-Max; ID: Study identification; SD: Standard deviation

DISCUSSION

This systematic review assessed the effectiveness and safety of ozone therapy for low back pain due to lumbar disc herniation. Most articles included showed improved results in both pain and functional status with therapies including ozone when compared to a control ozone-free group. This is in agreement with previous reviews, which showed similar results[10, 11]. Nevertheless, only 7 papers were included in the final synthesis, according to our strict inclusion criteria, and several limitations can be pointed out in these studies. First, different protocols were used in each study, with diverse ozone concentrations and doses, routes of application, and outcome assessment methods. Also, only two groups of two articles had the same generic comparisons, and even these performed with different methodologies, which precluded a quantitative analysis. All articles assessed evolution and/or resolution of pain complaints, but only 4 with comparable VAS evaluations. Additionally, disc hernia definition was absent from the majority of the included papers, as were the definitions of positive radiological outcomes. Most of the articles did not report on losses to follow-up and their management, on blinding and randomization and/or allocation methods, when applicable. Two previous systematic reviews are available on ozone application for LBP. One, in Spanish, also pointed out the low quality of the available data[10]. As in this review, the author states that positive results from this procedure were observed in patients with disc hernia, but these were based on inadequately performed studies with lack of standardization of techniques and assessment methodologies. Despite these weaknesses, these results were not very different from those observed with other infiltration techniques, and the conclusion was that better studies are needed to sustain the use of this therapy. The other review recommended ozone treatment in disc herniation[11]. However, this should be interpreted with caution, since only 4 articles with poor methodological approach supported these recommendations. When compared to a conventional microdiscectomy, ozone therapy failed to demonstrate any additional benefit, especially in extruded herniations, where ozone infiltrations are usually considered less effective or even contraindicated[13]. It has been widely reported that spontaneous improvement of pain and neurologic deficits is common in patients with disc hernia, and that the vast majority are able to return to work within three months from the onset of symptoms, without re-

TABLE II. COMPARISON BETWEEN EXPERIMENTAL AND CONTROL GROUPS

ID	Study times	Experimental Group	Control Group	Outcome Assessment			Side Effects
				Pain	Functional	Other	
Zambello, 2006	3w	Ozone: 5 mL (10-20 µg/mL)	Steroid (80mg)	↓*		NA	NI
	6m			↓*			
Bonetti, 2005	1w	Ozone: 3mL (25µg/mL)	Steroid (80 mg)	≈			
	3m			≈	NA	NI	
	6m			↓*			
Perri, 2016	2m	Steroid/Anesthetic + Ozone: 10 mL (28 µg/ml)	Steroid (4-6mg) + Anesthetic (2-3mL)	≈		MRI: ≠	NI
	4m			≈			
	6m			↓*			
Galluci, 2007	2w	Steroid/Anesthetic + Ozone: 10-14mL (28 µg/mL)	Steroid (80mg) + Anesthetic (2-4mL)	≈		NI	≈
	3m			≈			
	6m			↓*			
Paoloni, 2009	2w	Ozone: 20 mL (20µg/mL)	Sham Procedure	≈	Drug assumption: 👍* Kelner/SF-36/Backill: ≈	MRI: ≈	≈
	4w			≈	Drug assumption/Backill: 👍* Kelner/SF-36: ≈		
	6w			≈	Drug assumption/Kelner/SF-36: ≈ Backill: 👍*		
	3m			↓*	Drug assumption/Kelner/SF-36: ≈ Backill: 👍*		
	6m			↓*	Drug assumption/Kelner/SF-36: ≈ Backill: 👍*		
Paradiso, 2005	4-6m	Microdiscectomy	Ozone	NI	👎		NI
	1y			NI	👎	MRI/CT: 👎	
	3y			≈	👎	EMG: ≈	
Apuzzo, 2014	1m	Ozone	GPR	↓*		MRI: NC	NC
	1-5y			≈		MRI: NC Recurrence: 👍*	
	1m	Ozone + GPR	GPR	↓*		MRI: NC	
	1-5y			↓*		MRI: NC Recurrence: 👍*	

↓ Reduction of pain in experimental versus control; 👍 Better outcome in experimental versus control; 👎 Worse outcome in experimental versus control; ≈ Similar outcome in experimental versus control; ≠ Differences on MRI results were found but only as a tool to predict response to treatment; *Statistically Significant Differences; w: weeks; m: months; y: years; NI: No Information; NC: No Comparison; VAS: Visual Analogue Scale; SF-36: Short Form 36 Questionnaire; ODI: Oswestry Disability Index; MRI: Magnetic Resonance Imaging; CT: Computed Tomography; EMG: Electromyogram; GPR: Global Postural Re-education.

sorting to surgery[2]. Whether ozone infiltration actually influences the natural history of disc herniation is still a matter of debate. Ozone therapy is frequently cited as a low risk complication procedure[8]. Accordingly, ozone injections are proposed for patients with contraindications for surgery or as a temporary or exploratory pain relief therapy before surgical procedures[3,13]. Surprisingly, although ozone is regarded as a potentially toxic agent, very few studies actually report on the complications resulting from this therapy. These are mostly generic side effects: insomnia, itching, papules around the point of infiltration, gastritis, dizziness, tachycardia and hot flushes[11, 14]. Only three of the included references 3, 14, 15 explicitly reported on this. In two of them no complications were demonstrated in either study group, and in the other a low incidence

was reported with no differences between groups. Recently, serious infectious events related to ozone infiltration have also been published[16,17]. In an observational study of patients undergoing surgery for disc herniation or spinal stenosis, Vanni et al. reported the unexpected discovery of hard adhesions between the contracted root and the dural sac and/or fragmented disc, only in those previously submitted to ozone therapy[18]. This questions the idea of a totally safe procedure that can be attempted before surgery, and guidelines and protocols for its use should be better established. Ozone use in the medical field is currently not approved either by FDA or EMEA as there are no meta-analysis or multicentric studies to definitely prove its efficacy[16]. Still, it is widely prescribed in various countries of Europe, Asia and South America, and more than 3000 treatments are performed every day in Italy alone[18]. This review further reinforces the need of well-designed studies to provide adequate support for or against ozone treatment recommendations. This systematic review has some limitations. No quantitative assessment was performed due to the high heterogeneity of data. Also, neither a publication bias, nor a quality assessment were performed. Although one may infer the poor quality of the included studies, this analysis would increase the validity of our conclusions. Nevertheless, it is an appropriate summary of the current evidence available on this topic.

CONCLUSION

Little evidence is available on the effect of ozone injections in patients with low back pain due to lumbar disc herniation. However scarce and of poor quality, the studies gathered reported an improvement in pain and functional scores with its application. Complications, mostly minor, but potentially serious are underreported. Additional studies with adequate and consistent methodologies are needed before the role of ozone can be established in the management of low back pain.

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SUPPLEMENTARY FILE
PRISMA 2009 CHECKLIST

SECTION/ /TOPIC	#	CHECKLIST ITEM	REPORTED ON PAGE
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3; 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4; Table I
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4; Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4; Table II
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5; Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5; Table I
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA

Continues on the next page

CONTINUATION.

SECTION/ /TOPIC	#	CHECKLIST ITEM	REPORTED ON PAGE
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table II and II
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	5; Table II
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	5; 6; 7
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	5; 6
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	5; 6; 7
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12; 13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097; NA: Not applicable